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Nanopore electroporation for intracellular delivery of biological macromolecules

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We are pleased to see that simulation results by Mukherjee et al. (1) and Nathamgari et al. (2) are accordant with our experimental results (3). We also very much appreciate the detailed simulation study by Mukherjee et al. (1), specifically, on the prediction of the existence of an intermediate optimum voltage for transporting macromolecules. Although we agree with Nathamgari et al. (2) on the simplicity of the nanopore-electroporation system in allowing for an easy adaptation of the technology by the biological research community, the advantages of using the nanostraw system (4, 5) and single nanochannels (6) for uniform dosage control delivery could not be ignored, which would advance the discoveries in the biomedical research community. Regarding the so-called minor lapse that Nathamgari et al. (2) mention in the letter, the up to 50% transfection efficiency was reported in the 2014 paper (7) that we have cited, so there is no correction needed. We are aware that higher transfection efficiency (>70%) is reported in the latest publication by Mukherjee et al. (1). However, by the time the paper by Mukherjee et al. was published our paper had already been sent out by PNAS for external review. We also want to note that before sending the paper out for publishing we had filed a patent disclosure that was officially documented on 28 September 2018 (with the priority date of 18 March 2018). By showing the timeline of our publication and invention disclosure we hope to clarify that our publication represents our independent research along this direction.

- 1 P. Mukherjee, S. S. P. Nathamgari, J. A. Kessler, H. D. Espinosa, Combined numerical and experimental investigation of localized electroporation-based cell transfection and sampling. *ACS Nano* 12, 12118–12128 (2018).
- 2 S. S. P. Nathamgari, P. Mukherjee, J. A. Kessler, H. D. Espinosa, Localized electroporation with track-etched membranes. *Proc. Natl. Acad. Sci. U.S.A.* 116, 22909–22910 (2019).
- 3 Y. Cao et al., Nontoxic nanopore electroporation for effective intracellular delivery of biological macromolecules. *Proc. Natl. Acad. Sci. U.S.A.* 116, 7899–7904 (2019).
- 4 X. Xie et al., Nanostraw-electroporation system for highly efficient intracellular delivery and transfection. *ACS Nano* 7, 4351–4358 (2013).
- 5 Y. Cao et al., Universal intracellular biomolecule delivery with precise dosage control. *Sci. Adv.* 4, eaat8131 (2018).
- 6 P. E. Boukany et al., Nanochannel electroporation delivers precise amounts of biomolecules into living cells. *Nat. Nanotechnol.* 6, 747–754 (2011).
- 7 W. Kang et al., Microfluidic device for stem cell differentiation and localized electroporation of postmitotic neurons. *Lab Chip* 14, 4486–4495 (2014).